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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,005	10/29/2001	Gary L. Nelsestuen	09531-016002	3846

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EXAMINER	
SCHNIZER, HOLLY G	
ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 10/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,005	NELSESTUEN, GARY L.	
	Examiner	Art Unit	
	Holly Schnizer	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-115* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *112* is/are allowed.

6)☒ Claim(s) *76-77,79,83-94,96-99,101-104,110,111,114 and 115* is/are rejected.

7)☒ Claim(s) *78,80-82,95,100,105-109 and 113* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/7/02&7/19/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

The Preliminary Amendment filed 12/22/03 has been entered. Claims 1-75 have been cancelled. Claims 76-115 have been added. Therefore, Claims 76-115 are pending and have been considered in the Office action below.

Objections to the Specification

The Specification is objected to because the Brief Description of the Drawings refers to panels A, B, and C for Figure 15 that are not found in the drawing (see p. 8, lines 30-33).

Priority

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). To fulfill the requirements to claim benefit to prior applications, Applicant should state such a benefit claim in the first line of the specification (see MPEP 201.11).

Claim Rejections - 35 USC § 112

Claim 84, 96, 97, and 110 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 84 is improperly dependent since it depends from itself. Thus, the claim is confusing because there is a lack of antecedent basis for "The polypeptide" and the identity of the polypeptide is unclear. It appears that Claim 84 was intended to be dependent from Claim 83 and the claim will be interpreted this way for purposes of this Office Action. However, correction to provide proper dependency is required.

Claims 96 and 110 are indefinite because the claims do not recite what effect the factor VII or factor VIIa is intended to have and thus the metes and bounds of "effective amount" are unclear. Claims 97 is rejected since it is dependent from Claim 96 yet does not correct its deficiencies.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 76-77, 79, 85-89, 93, 94, 98, 101-104, 111, and 114-115 rejected under 35 U.S.C. 102(b) as being anticipated by Cheung et al. (Thromb. Res. (1995) 79(2): 199-206).

Cheung et al. disclose factor VII polypeptides comprising modified GLA domains wherein the modified GLA domains comprise an asparagine substitution (a hydrophobic amino acid) at position 33 and a threonine substitution (a hydrophobic amino acid) at position 34 (see p. 202, Fig. 1, mutants 1-8) as well as substitutions at positions 10

(mutant 4 contains a glutamine substituted at position 10) and 32 (mutants 1-8 contain a glutamic acid substituted at position 32), and an insertion of glycine at position 4 (mutants 3, 5, 7, and 8). Cheung et al. also teaches nucleic acid molecules encoding these mutant factor VII proteins, host cells containing the nucleic acid molecules, and methods of making the proteins (see Materials and Methods, pp. 200-201).

Cheung et al. do not teach that the mutant factor VII disclosed therein have enhanced membrane binding affinity relative to the corresponding native factor VII (sequence shown in first line of figure 1). However, the issue at hand is not whether Cheung et al. knew that the mutant protein had properties presently claimed but whether Cheung et al. disclose a product that is patentably indistinguishable from that presently claimed. The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. (see MPEP 2111.03 and In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977 cited therein). In the present case, the factor VII mutants of Cheung et al. meet all of the structural limitations of the claims. The functional properties of a protein are dependent on its sequence. Therefore, it would be inherent that the mutants of Cheung et al. would have the claimed functional characteristics (enhanced membrane binding affinity). Cheung et al. teach that the mutant proteins bind to a factor VII monoclonal antibody and suggest that the folding of factor VII is not disturbed by the mutations (p. 202, 1st paragraph). The factor VII mutants of Cheung et al. have substitutions that enhance membrane binding affinity (the substitution of Gln at position 10 for example). Moreover, the factor VII mutants of Cheung et al. have additional mutations all of which

are changes from a human factor VII amino acid to a human factor IX amino acid at the corresponding position. The factor IX Gla domain has enhanced membrane binding as compared to that of Factor VII, therefore, it would be inherent that a factor VII protein with a Gla domain more closely resembling that of factor IX would have enhanced membrane binding affinity. Furthermore, there is a correlation between membrane affinity and net negative charge of the surface amino acids and the Gla domain of the Cheung et al. mutants has a more negative net charge than the native human factor VII, which is correlated with enhanced membrane binding affinity, and it has a sequence more closely resembling human factor IX, which has enhanced membrane binding affinity than factor VII. Thus, the factor VII mutants of Cheung et al. have all the structural limiations of the claims and inherently have all of the functional limitations of the claims.

Claims 76, 83, 96, 98, 101, and 102 are rejected under 35 U.S.C. 102(b) as being anticipated by Persson et al. (FEBS Letters (May 1996) 385: 241-243; ref. AAAA of IDS filed June 7, 2002).

Persson et al. teaches a factor VIIa polypeptide comprising a substitution at position 35. Persson et al. teaches that position 35 was substituted with Asp, Gln, and Val . Valine is considered a hydrophobic amino acid. Therefore, Persson et al. teaches a factor VIIa having the same structure encompassed by the claims. The function of a protein is an inherent property of its structure. Therefore, it appears that the mutants of Persson et al. would have enhanced membrane binding affinity, absent evidence to the

contrary. Persson et al. also teaches nucleic acid molecules encoding the mutant factor VIIa polypeptides (section bridging pp. 241-242), mammalian host cells expressing the polypeptides (baby hamster kidney cell line; p. 242, Col. 1, Section 2.3), and methods of making the polypeptides (p. 242, Col. 1, section 2.4). The polypeptides of Persson et al. are purified into a buffer and, absent evidence that any components of the composition would be harmful if administered to a subject, the composition containing the polypeptide is considered a pharmaceutical composition (where the buffer is considered the pharmaceutically acceptable carrier).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 76-77, 85, 90-92, 96-97, and 99 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6.017,882.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Claim 1 of U.S. Patent No. 6,017,882 recites a vitamin K-dependent polypeptide comprising a modified GLA domain that enhances membrane binding affinity of said polypeptide relative to a corresponding native vitamin K-dependent polypeptide, said modified GLA domain comprising at least one amino acid substitution at residue 11, 12, 29, or 34, and wherein said polypeptide increases clot formation. It is noted that the residue numbers of Claim 1 of USP 6,017,882 are based on the protein C sequence and correspond to positions 10, 11, 28, and 33 of SEQ ID NO:3 of the present Application. Claims 2 and 4-5 of USP 6,017,882 further define the position substituted, Claim 3 defines an inherent property of the polypeptide, Claims 6-8 are drawn to pharmaceutical compositions comprising the polypeptides, and Claim 9 is drawn to a method of increasing clot formation using the polypeptides. Claims 1-9 differ from the present claims herein in that they are drawn to the genus of vitamin K-dependent proteins and not the specific members such as Factor VII claimed herein. Claims 1-9 also differ in that they include the additional limitation that the polypeptide must increase clot formation. Claims 1-9 differ from the dependent claims herein in that it fails to recite

the specific amino acids to be substituted at the specific positions claimed. However, U.S. Patent No. 6,017,822 teaches that factor VII is a vitamin K dependent polypeptide that may be modified to enhance membrane binding affinity (Col. 7-8 and Ex. 1 and 2) and that modifying factor VII would provide the benefit of lowering the dosage necessary in treatment (Col. 2, lines 35-40). U.S. Patent No. 6,017,822 also teaches that substituting glutamine, glutamate or aspartate at position 10; phenylalanine at position 28; and/or glutamine or aspartate at position 33 (all positions relative to the factor VII sequence) would result in the desired effect (enhancement of membrane binding; see Col. 7, lines 30-50 and Col. 8, lines 24-29). Moreover, specifically substituting glutamine at position 10 and glutamate at position 32 is disclosed as resulting in a polypeptide with much higher affinity for membranes and having much higher activity in autoactivation, in factor Xa generation and in several blood clotting assays (Col. 7, lines 55-57). Therefore, it would have been obvious to select factor VII from the vitamin K dependent proteins claimed in U.S. Patent No. 6.017,882 and make the specific amino acid changes claimed in the present application. One having ordinary skill in the art would have been motivated to choose factor VII and the specific modifications presently claimed since U.S. Patent No. 6, 017, 882 teaches that these modifications result in enhanced membrane binding and that enhanced membrane binding in factor VII would be desirable since it would allow for administration of lower doses of factor VII in therapy.

The examiner acknowledges that a restriction requirement was made in the parent application, however, the restriction appears to have been made subject to non-

allowance of a generic claim (see Paper No. 3 in Appl. No. 08/955,636, see specifically p. 4, lines 12-14 of the Office Action) and the generic claim (to vitamin K-dependent polypeptides) was allowed. Thus, the double patenting rejection above applies.

Objections

Claims 78, 80-82, 95, 100, 105-109, and 113 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusions

Claims 76-77, 79, 83-94, 96-99, 101-104, 110-111, and 114-115 are rejected. Claims 78, 80-82, 95, 100, 105-109, and 113 are objected to. And, Claim 112 is in condition for allowance. There is no teaching or suggestion in the prior art of a method of increasing clot formation in a mammal comprising administering modified factor VII or factor VIIa comprising an insertion at position 4 according to SEQ ID NO:3.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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September 29, 2005

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